Antiadenovirus activity of new fluorine-containing polypeptides mimetics

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Abstract: More than 60 serotypes cause a variety of courses and severe clinical signs of infectious disease. However, there is no specific drug for the treatment of adenoviral diseases. The studying of fluorinated nucleoside sugars chemistry became the basis for the development of promising chemotherapeutic agents with antitumor and antiviral effects. Based on the purine and pyrimidine nucleotide analogs and fluorinated heterocycle molecules a number of new generation drugs with anticancer effect was developed.

The reference strain of human adenovirus serotype 5 and monolayer cell line MDBK were used in the experiment. We studied new fluorine-containing compounds 10S-25 (1-S-thio-(1-methylsulfonyl-2-difluoromethyl-vinyl)-2,3,4,6,-tetra-O-acetyl-β-D-glucopyranose), 10S-26 ((S)-2-(ethoxydifluoromethyl)-pyrroldine hydrochloride), 10S-27 (1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole), 10S-28 (Dimethyl N,N'-(2,2-difluoropropanedithiyl)bis(L-alaninate)), synthesized in Institute of Organic Chemistry of the NAS of Ukraine. Antiviral activity and the effect on adenovirus synthesized de novo were investigated.

Cytotoxicity of experimental compounds was within 16 - 637 μg/ml. Antiviral activity was maximal for compound 10S-27 in the concentration of 16 μg/ml (36%). Other experimental compounds had less antiviral activity in all concentrations. However, they had a significant influence on the synthesis of viral offspring. The percentage of virus inhibition titer was in the range of 65-92%. Therefore, the experimental compounds affected the formation of the infectious viral offspring.

Keywords: adenovirus, fluorine-containing compounds, antiviral activity.
Introduction

- Human adenoviruses cause various acute diseases including gastrointestinal and respiratory disorders.
- However, there are no clinically approved specific anti-adenoviral drugs.
- Based on the purine and pyrimidine nucleotide analogues and fluorinated heterocycle molecules a number of new generation drugs with antiviral and anticancer effect were developed.
- Therefore, the search of drugs and regimens that would be effective, safe for prolonged use, and available at a cost for a wide range of patients is extremely important.
Test compounds

Novel fluorine-containing compounds were studied:

- **10S-25**(1-S-thio-(1-methylsulfonyl-2-difluoromethyl-vinyl)-2,3,4,6,-tetra-O-acetyl-β-D-glucopyranose),
- **10S-26** ((S)-2-(ethoxydifluoromethyl)-pyrrolidine hydrochloride),
- **10S-27** (1-(β-D-glucopyranosyl)-4-(hexafluoropropyl)-5-tosyl-1H-1,2,3-triazole),
- **10S-28** (Dimethyl N,N'-(2,2-difluoropropanedithioyl)bis(L-alaninate)), synthesized in Institute of Organic Chemistry of the NAS of Ukraine.
Cytotoxicity of the compounds was determined by MTT-test according to the standard protocol.

Inoculated cell culture MDBK (bovine kidney) were used for this procedure.

Cytotoxicity of experimental compounds was within the range of 16 - 637 μg/ml.
Antiviral activity of tested compounds

(\textit{was determined by MTT-test})
Influence of the compounds on virus synthesized *de novo* (was determined by MTT-test)
Discussion

• The test compounds showed low antiviral activity.

• However, the effect of the compounds on the titer of the virus synthesized de novo indicates that the compounds affect the formation of infectious virus progeny.

• As a result, it can be assumed that fluoride-containing mimetics affect the viral DNA. Although virus offspring are formed, virus particles are not complete, and they are not able to cause an infection process.
Conclusions

• The cytotoxicity of fluorine-containing compounds 10S-25, 10S-26, 10S-27, 10S28 was studied. CC\textsubscript{50} indexes were within the range of 16 - 637 µg/ml.

• Antiviral activity against adenovirus serotype 5 was also investigated. Percentage of inhibition of the virus ranged from 3 to 36 %.

• Fluorinated mimetic polypeptides showed a significant inhibitory effect on the virus titer synthesized \textit{de novo}. Percentage of inhibition was in the range of 60-92%.